corresponding "SEQ ID NO."

Reconsideration of the rejection of claims under 35 USC §112, ¶2, for use of "modified . . . molecule" is requested. The remainder of the rejected claims defines the "modified" molecule. It is applicants' prerogative to define their invention, not the examiner's. *In re Pilkington*, 162 USPQ 145, 148 (CCPA 1969).

Reconsideration of the rejection of claims under 35 USC §112, ¶2, for reasons other than use of "modified," are resolved by the changes to the claims effected, hereby.

Claims were rejected under 35 USC 112, ¶1, for allegedly lacking enablement. Reconsideration is respectfully requested.

According to the statement of rejection the prior art and the present specification fail to establish a nexus between the release or activity of TNFα and the development of cancer, disseminated sclerosis, psoriasis, osteoporosis, or asthma. Applicants do not agree for the following reasons, with respect to the various diseases .

(a) Cancer: US 5,691,382 claims a method for inhibiting the effects of TNF in various conditions, including cancer (cf. claim 18). Thus, the USPTO has allowed that anti-TNF therapy is useful in the treatment of cancer. However, two aspects of the use of anti-TNF therapy need to be distinguished.

The first, which the Examiner has' considered, is the effect of TNF on tumor growth. The Examiner seems to have taken the name "tumor necrosis factor" to be an accurate and full description of the function of the protein. This is, however, not correct. TNF was originally described as a factor causing necrosis of some tumor cell lines, but it appeared that it was not toxic to all tumor types, and, furthermore, it is not the body's

only mechanism for eliminating tumors. The enclosed abstracts 1-5 concern studies in which TNF acts as a growth promoting agent for tumors. Abstract 1 (last sentence) suggests that anti-TNF therapy could be useful in malignant myeloma.

The second proposed utility of anti-TNF therapy is not the prevention of tumor progression but is the reduction of the effects on the body of the disease, and in particular on the cachexia associated with cancer. It is well known that TNF does contribute to this wasting phenomenon. Thus, anti-TNF therapy could be used to combat weight loss in cancer and hence be of benefit even in cases where the tumor is not growing in response to TNF.

(b) Disseminated sclerosis: A possible point of confusion here is that disseminated sclerosis is synonymous with multiple sclerosis and so it might not be immediately apparent that there is a significant amount of background material available. To cite only the most directly relevant, US 5,958,409 (WO 98/03827) is directed to a method of treating multiple sclerosis by anti-TNF therapy.

(c) Psoriasis: US 5,619,382 mentioned above also relates to psoriasis as a therapeutic target for anti-TNF therapy (cf. in particular claim 18). Cf. also claim 8 of US 5,563,143.

(d) Osteoporosis: The enclosed abstracts 6-10 form leading references to work that implicates TNF in the pathophysiology of osteoporosis. In particular, abstract 9 shows that neutralizing endogenous TNF protects against bone loss in an experimental model of menopause.

(e) Asthma: Claim 8 of the above-cited US 5,563,143 also identifies asthma as a

target for anti-TNF therapy.

Accordingly, the requirements for enablement are satisfied by the instant specification. In order to satisfy the requirements of §112, first paragraph, "it is not necessary to embrace in the claims or describe in the specification all possible forms in which the claimed principle may be reduced to practice." *Smith v. Snow*, 294 U.S. 1, 11 (1935). The law does not require an applicant to describe in his specification every conceivable embodiment of the invention. *SRI Int'l v. Matsushita Elec. Corp. of America*, 227 USPQ 577, 586 (Fed. Cir. 1985). "In satisfying the enablement requirement, an application need not teach, and preferably omits, that which is well known in the art." *Staehelin v. Secher*, 24 USPQ2d 1513, 1516 (BPA & I 1992).

Claims were rejected under 35 USC 103 for allegedly lacking patentability over the combined teachings of Mouritsen and Eisner with Pennica *et al.,* Shirai *et al.,* or Wang *et al*, further in view of Jones, and/or further in view of Pannina-Bordigon. Reconsideration is requested.

Applicants cite the reference Van Ostade et al., *Nature 361*,266-269 (1993), which was cited In the response to the Second Written Opinion, during the international phase. The discussion given in the responses to the First and Second Written Opinion applies equally well to the references cited in the §103 rejection, i.e., Pennica et al., Shirai et al,, Wang et al, and Panina-Bordigon et al.. The TNFα DNA sequence has been described by Wang et al, cf. the description page 15. The complete TN-Fa gene sequence was described by Shirai et al. and Pennica et al., respectively, cf. page 16 of the description.

From such descriptions, however, the skilled artisan could not have predicted which

part(s) of the sequence is(are) to be modified. Panina-Bordigon et al. disclose applicable T-cell epitopes, cf. page 22 of the description. However, there is no guidance where to insert such epitopes. The prior art must be enabling to show obviousness. *In re Irani*, 166 USPQ 24 (CCPA 1970).

The presently claimed invention provides a set of concise guidelines for the skilled person wishing to prepare an immunogenic TNFα variant which is capable of raising neutralizing antibodies against human TNFα. In preferred embodiments, the TNFα variant is furthermore detoxified, cf. the Subject matter of claim 2. Hence, the antibodies induced according to the presently claimed invention are capable of neutralizing the activities (e.g. the cytotoxic activity) of human TNFα. This is e.g. opposed to the alternative, namely to enhance clearance of TNFα.

The disclosure by Mouritsen and Eisner teaches a generally applicable method for preparing immunogenic analogues of self-proteins, thereby enabling induction of self-reactive antibodies. In examples 3 and 4 in Mouritsen and Eisner, examples are given of successful immunization of mice with analogues of murine TNFα. However, there is no disclosure in Mouritsen and Eisner which deals with the question of whether the antibodies induced neutralise the biological activity of TNFα or not.

Therefore, what is taught in Mouritsen and Eisner is that it is possible to prepare variants of murine TNFα, which are immunogenic in mice by means of careful introduction of selected foreign T-cell epitopes in murine TNFα. Further, since all tested constructs in Mouritsen and Eisner are effective in that regard, the expectation which can be inferred from Mouritsen and Eisner is therefore simply that the same would hold true for human

TNFα. Mouritsen and Eisner does not, however, contain any disclosure of data which can provide any information as to the ability of the murine vaccines to neutralize murine TNFα.

Therefore, applicants submit that it would require undue experimentation by the skilled artisan even to identify variants of murine TNFα which are capable of neutralizing the biological activity of murine TNFα.

Furthermore, when the skilled person faces the problem of providing an immunogenic variant of human TNFα which 1) can induce neutralizing ant. i-TNFα antibodies in humans and which 2) is biologically inactive, he is actually facing conflicting objectives. To prepare a biologically inactive human TNFα variant, it is necessary to somehow destroy the receptor-binding properties so that the variant will not itself be capable of exerting the biological activity of TNFα - this is, e.g., apparent from Mouritsen and Eisner, page 7, lines 11-15.

On the other hand, when attempting to prepare a variant of human TNFα which is capable of raising neutralizing antibodies, it is desirable to preserve B-cell epitopes from parts of the molecule involved in receptor binding, since these are the very B-cell epitopes against which the immune response should be directed, cf. the explanation on page 18, lines 18-26 in the present specification.

Given this background, it is not altogether clear why the discussion in Mouritsen and Eisner concerning provision of detoxified, immunogenic variants of murine TNFα could be relevant for the obviousness of a variant of human TNFα which is capable of inducing neutralizing antibodies, such as the variants recited in claim 1.

The presently claimed invention demonstrates that there are regions in the human

TNFα molecule which are not suited for introduction of foreign T-cell epitopes. When preparing variants thereof with a view to making a vaccine which can induce neutralizing antibodies. As can be seen from Example 4 in the specification, not all tested human constructs proved to induce the production of neutralizing antibodies against TNFα. Notably, it could be demonstrated that constructs TNF2-4, TNF2-1, TNF30-1 and TNF30-4, which all contain substitutions in the G and B strands of the back β--sheet, were unable to induce antibodies capable of neutralizing the biological activity of TNFα.

Furthermore, it was demonstrated that at least one construct, TNF2-5, was superior compared to other constructs in inducing neutralizing antibodies.

None of these findings are taught, suggested or hinted at in Mouritsen and Eisner, and for these reasons alone it is impossible for a combination of Mouritsen and Eisner with any or all of Pennica *et al.,* Shirai *et al..,* and Wang *et al.* to teach the invention as presently claimed. Claim 1 requires that certain regions of the human TNFα molecule be subject to substitutions, and this specific requirement cannot be extracted from any of the cited prior art references, neither alone nor in combination. It would require undue experimentation for the skilled person to arrive at the presently claimed subject matter, thus rendering improper the rejection under §103. *Irani, supra.*

At any rate, the subject matter of present claim 4 includes a requirement that two specific β-sheet structures of human TNFα are essentially preserved. This teaching is neither derivable from Mouritsen & Eisner (which does not exclude any part of murine TNFα) nor from any of the references Pennica *et al.,* Shirai *et al.,* and Wang *et al.*

The Examiner has also cited Jones *et al.* However, the Examiner uses this reference

while focusing on the ability of the resulting construct to lack the ability to bind to the TNF receptor, i.e. he focuses on the detoxification of the construct, cf. the paragraph bridging pages 11 and 12 in the Office Action. However, the Examiner does not explain how the skilled person could expect to arrive at an antigen capable of inducing neutralizing antibodies by "... substituting a region of functional importance in the TNFα molecule for receptor binding...". Applicants submit that the skilled person would consider that a construct made on this background would be most unlikely to provide for neutralizing antibody production, because it lacks the receptor binding portions against which antibodies are desirable.

Favorable action is requested.

Respectfully submitted,

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